Envelope-to: colman@ican.net
Date: Tue, 4 Jan 2000 10:29:55 +0100 (MET)
X-Sender: emartin@mailhost.pasteur.fr
To: colman@ican.net
From: Edith MARTIN <emartin@pasteur.fr>
Subject: To John Scythes

Dear Dr. Scythes,
Thank you for your recent e-mail.
Luc Montagnier

Envelope-to: colman@ican.net
Date: Tue, 4 Jan 2000 14:07:44 +0100 (MET)
X-Sender: isgirons@mailhost.pasteur.fr
To: John Scythes <scythes@colman.net>
From: Isabelle Saint Girons <isgirons@pasteur.fr>
Subject: Re: poster for Gordon conference
Cc: bockenstedt@yale.edu

Dear dr Scythes,
Thank you for your detailed answer and for promoting your colleague J. Podwinska. We have scored the posters now and have chosen those for the late breaking session.
we are looking forward to discussing with you in Ventura,
Isabelle

Isabelle Saint Girons
Unite de Bacteriologie Moleculaire et Medicale,
Institut Pasteur, 28 rue du Docteur Roux,
75724 Paris Cedex 15, FRANCE.
Tel: +33 1 45 68 83 66
Fax: +33 1 40 61 30 01

To: Luc Montagnier
From: John Scythes <mail@colman.net>
Subject: To: Luc Montagnier
Cc:
Bcc:
Attached:

Please forward this message to Dr. Montagnier.

Dear Dr. Montagnier,

I thought I would just give you a brief update of the syphilis co-factor thinking. I have been trying, as you know, to get more sensitive syphilis screening, based on recombinant antigens, into areas where the HIV crisis could be described as "emerging". Looking at the studies from Rakai and Mwanza, we think that aggressive control of STDs can influence not only the incidence of HIV, but also the progression of the syndrome. I have always felt that syphilis control is an intimate part of this intervention strategy, not only because of the ulceration, but also because of the immuno-regulatory effect of latent syphilis against Th1, treatment notwithstanding.

I have been accepted as an attendee at the Gordon Conference 2000 on the Biology of Spirochetes, taking place in January in Ventura, California, where I will continue my efforts to interest some of the regular American and European syphilis researchers in a multi-factorial approach to AIDS. My Polish colleague of many years, Dr. Jadwiga Podwinska (who works in the Laboratory of Medical Microbiology, Department of Immunology of Infectious Diseases, at the Institute of Immunology and Experimental Therapy in Wraclaw) will be joining me at the meeting. She has, for the first time ever, looked at the cytokine profiles during *human* latent syphilis. It seems that once the disease has been allowed to persist untreated into its latent stages, a Th2 cytokine picture emerges, which cancels immunologic memory to syphilis (and perhaps to other infections) and which cannot be reversed by treatment. These findings seem to contradict those of Lukehart and others from the University of Washington in Seattle.

I will also try my best to interest American centers in re-establishing syphilis animal models, with a view to investigating whether or not AIDS can be induced by repeated exposures to T. pallidum. There are several hundred primates languishing in HIV research centers around the U.S., and perhaps an exposure or two to T. pallidum would induce AIDS, or at least activate the viral expression/progression to AIDS, in these animals. It may also be possible to have a much more affordable AIDS animal model, as both hamsters and guinea pigs are good models for latent syphilis.

I enclose below a letter, sent October 1, 1999 by regular mail to the Task Force for the Urgent Response to the Epidemics of Sexually Transmitted Diseases in Eastern Europe and Central Asia, based at the WHO Regional Office for Europe in Copenhagen. This letter explains some of my current thinking about co-factors and better syphilis testing. Electronic copies were also sent to Drs. Alex Gromyko and Andre Meheus, both of whom I have met a number of times at STD meetings. I have not received a reply, but I realize they are under no obligation to respond or to take an interest in these views.

If things were going a little better, from the point of view of an affordable public health intervention for AIDS - i.e., a vaccine that really worked - then all our points about co-factors preparing the way for the HIV process might be mute. But from everything I have been able to gather from the VAXGEN work, and

indeed from all the past vaccine initiatives, it looks like we may be many years away from a successful HIV vaccine, if indeed this proves possible. You might be interested in reading a feature article that appeared in the Sunday Times on October 3, written by Brian Deer. It is available on the World Wide Web at
http://www.newstrolls.com/news/dev/guest/101199.htm
While it is a summary for the lay reader, it does contain some good scientific points and various views, both for and against Francis' initiative.

Best wishes for the holiday season and a smooth transition to the next millenium.

Sincerely,

John

October 1, 1999
Task Force for the Urgent Response to the Epidemics of Sexually Transmitted Diseases in Eastern Europe and Central Asia (TF/STD),
Department of Infectious Diseases,
WHO Regional Office for Europe,
8 Scherfigsvej,
DK-2100
Copenhagen Ø
Denmark

Re: Possible interaction of STDs and subsequent HIV seroconversion/AIDS

Dear Task Force:

Having read the on-line report of the 1-2 June 1999 Third Meeting of the TF/STD, and at the suggestion of Dr. Meheus, I respectfully submit a request to participate in the next TF/STD meeting. I would like to present my emerging views on immuno-regulation in syphilis, which suggest that untreated/inadequately treated infection with T. pallidum is not only a co-factor for HIV transmission, but also plays an important (and possibly necessary) role in the development of AIDS itself.

Since 1987, I have written a certain amount on this subject, and also have published, i.e. co-authored, five reviews of syphilis serology in HIV-infected homosexual cohorts, three times at the Toronto Hospital, and twice at the Semmelweis Medical School, and I enclose my CV, which lists these reviews and my speaking engagements.

Also enclosed is a grant application made by colleagues of mine to the Canadian Foundation for AIDS Research (CANFAR) in 1994, which outlines several possible research directions for investigating the possible role of occult syphilis in HIV disease. This was not funded.

In 1996, along with my colleague Colman Jones, I submitted another grant application to George Soros' Open Society Institute (OSI) for funds to investigate the possible role of latent syphilis in an HIV-infected cohort at the Semmelweis outpatient Dermatology clinic (OBNI) in Budapest, with the permission of the clinic.

We were not given any funds by the OSI, but we remain concerned that some variation of the approach described in the accompanying applications will shed some light on the direction that your task force might take, from a practical and affordable public health point of view, to slow the emerging HIV crisis. A project like this needs to be done in an area where there is an emerging, rather than established, pattern of HIV/STD interaction, along the lines of the Mwanza vs. Rakai situations.

Our basic concept is that by stopping syphilis, or at least slowing it down, far fewer people will become HIV-infected and/or develop AIDS - but not just because of fewer opportunities for transmission of the virus. I respectfully suggest that syphilis represents more than simply an ulcerative or focal activation phenomenon in HIV acquisition/AIDS. Syphilis may also turn out to be an important immunologic co-factor for susceptibility to active viral expression and progression to AIDS.

I agree with the position that early syphilis in a naïve population can be successfully diagnosed and cured most of the time within our current paradigm for the management of the disease. I am suggesting you consider the problem of latent syphilis, when the disease has gone untreated or inadequately treated for some highly variable period of time, a phenomenon which has simply not been investigated in modern times in terms of its immunologic consequences.

Syphilis is rarely inactive and the word "latent" is a misnomer, at least in how we seem to understand it from standard medical teaching. Latent means hidden in Latin, not inactive. Latent syphilis is chronic active syphilis from the immunologic standpoint, and is both more dangerous for immune system genetics and harder to treat than exanthematous late syphilis. Judging from the work of Poland's Jadwiga Podwinska and the late Tom Fitzgerald from Minnesota, a Th2 cytokine pattern begins to predominate in most persons with latent syphilis, and standard treatment does not reverse this phenomenon. Subsequent re-exposure without Th1-driven immunologic anamnesis would lead to the silent re-dissemination of treponemes. Syphilis animal research strongly supports the concepts of silent re-infection with T. pallidum and the lack of anamnestic response - whether DTH or antibody - upon re-exposure.

As a result of this failure of immunologic memory, it is likely that the current non-treponemal screen tests used in many centers are insensitive in populations at risk for multiple exposures to T. pallidum. The Wassermann-type tests seem reliable in the naïve populations, but often fail to detect re-infection/relapse, a view now adopted by the U.S. Centers for Disease Control (posted on the Internet at http://www.cdc.gov/ncidod/dastlr/gcdir/index.html#TPlink). As well, recent findings in the diagnosis and treatment of late Lyme disease suggest important precedents for our understanding of latent syphilis.

It is my view that silent re-infection with syphilis plagued Western homosexual populations during the late 1970s and early 1980s, and is now spreading in the 1990s among the heterosexual at-risk populations in many Eastern European centers. I am very concerned that without a better syphilis control strategy - i.e., a possible preventative vaccine and better testing and follow-up for early disease - many people in Eastern Europe and Central Asia will die as a consequence of genetic immune deviation in response to re-exposure to T. pallidum, manifesting itself as AIDS and HIV activation. Indeed, we see the HIV seroconversion curves in Russia closely following the syphilis epidemic - as happens everywhere in the world.

When I was in Göteborg, participating in the 1998 IUSTI, I met Dr. A. Gromyko, and subsequently visited him at the Copenhagen offices. We had a detailed and cordial discussion on many of the points raised in this correspondence. If you are willing to entertain this hypothesis further, I will come to Copenhagen at my expense and review our published Toronto Hospital findings, and present my interpretation of the historical literature on experimental syphilis.

As well, from the practical point of view of where to go next, I will suggest a recombinant treponemal antigen-based screening system be used alongside the traditional techniques in a prospective investigation, a project that could be enhanced by external support. Here in the Toronto area, my colleague of many years, Dr. Robert Notenboom at Phoenix Biotech in Mississauga, Ontario (e-mail: bnotenboom@phoenixbiotech.com), has been developing these newer tests and there is a building literature on the improved sensitivity offered by such a system (see Erbelding, E.J. et al., Journal of Infectious Diseases, November 1997, vol. 176(5), pp. 1397-1400). The recombinant system compares favourably with existing techniques from the cost point of view.
Dr. Bruno Schmidt at the KH Lainz has run Notenboom's tests this past summer in a panel of sera that he described as 'difficult', and found considerably better sensitivity. Currently, Dr. Karoly Nagy at the Semmelweis is retesting his HIV cohort with these techniques, comparing the results with Organon Teknika's treponemal tests. However, the HIV and STD interaction pattern in Budapest and Vienna is relatively established, with only a few new syphilis cases each year in each clinic. We would very much like to see these tests run in a center where syphilis is epidemic, and continue using them for a 5-year period on all follow-up visits, with special emphasis on the response to these antigens in persons with HIV.

I hope this is of interest to the Task Force, and look forward to hearing from you. You may communicate with me by electronic mail via colman@ican.net, or by regular post.

Yours sincerely,

John B. Scythes
32 Beaty Avenue
Toronto, Ontario
M6K 3B4
Canada

Enlcs.